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Sample size for a pilot randomised trial to minimise the overall trial sample size for a continuous outcome variable

Whitehead AL ,Campbell MJ*, Julious SA and Cooper CL

Medical Statistics Group ScHARR, University of Sheffield

*Contact: m.j.campbell@sheffield.ac.uk

Sample size requirement

- A sample size calculation for a trial with a continuous outcome should specify the Type I error, the Type II error or the power, the effect size and the variance of the outcome measure.
- Type I and Type II errors are generally fixed. The effect size should be specified *a priori* as a minimum clinical difference, so the main uncertainty is about the variance.

What this talk covers

- Scenario : External pilot, and then a main trial
- Design the pilot trial to estimate the variance of outcome of the main trial to inform the sample size calculation
- Assumes pilot and main trials have the same outcome.
- Would like to minimize the total number of patients involved.

Outline

Variance from pilot is estimated with uncertainty.

Big pilots=> less uncertainty but more patients

1) Review two methods to allow for this: the upper confidence limit methods and the non-central t method
2) Use search technique to find pilot sample size which minimises total

Upper Confidence Limit (UCL) method

1. Find the variance in the pilot with k degrees of freedom.
2. Find the 100X% UCL for the variance, and use this in the sample size calculation
3. Revised variance given by

$$s^2_{UCL} = \left[\frac{k}{\chi^2_{1-X,k}}\right] s^2$$

For a two arm pilot k=2m-2, m is size per arm.

UCL method (2)

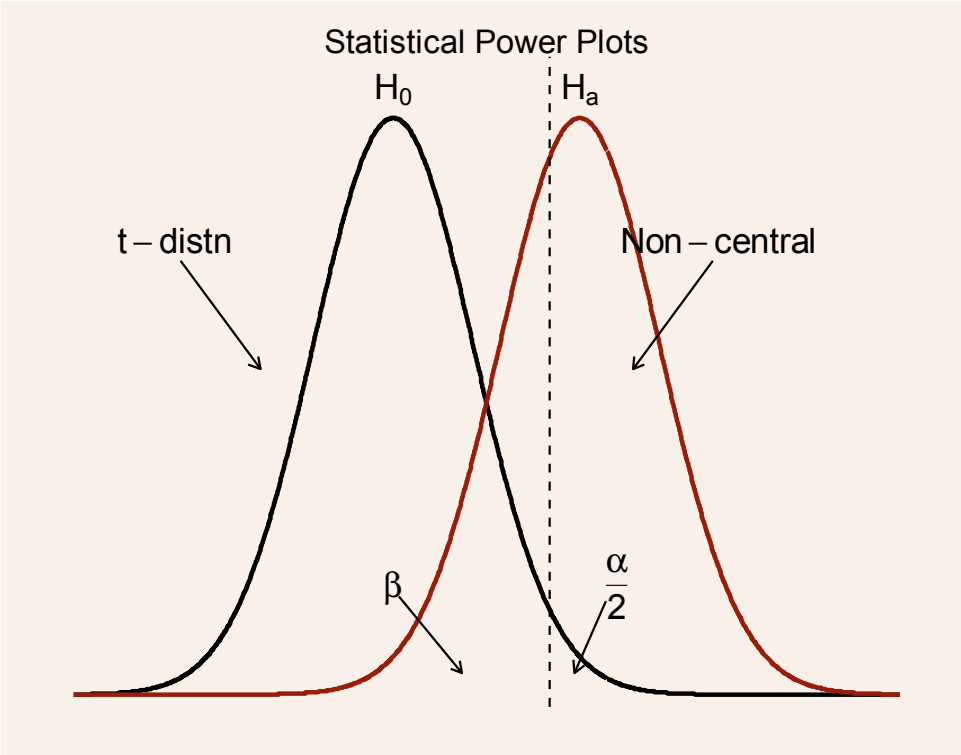
- Browne(1995) suggested X=80%
  - If pilot k=20, inflate the sample size of trial from standard if we knew the variance by 40%
- Sim and Lewis(2012) suggested X=95%
  - If pilot k=20, inflate sample size of trial by 90%

Non-central t-approach(1)

Julious and Owen (2006) suggest an alternative method for the calculation of sample size accounting for the fact that we are using a sample estimate of the standard deviation rather than the population standard deviation in the calculation.

They use a non-central t distribution based on k degrees of freedom and non-centrality parameter based on the central t distribution.

Non-central t-approach(2)



Under H_0 the standardised difference d is distributed as a t distribution with 2n-2 df.
Under H_a d is distributed as a non-central t with non-centrality parameter $t^{-1}(1-\alpha/2, 2n-2, 0)$

Non-central t approach –two arm trial

- Julious and Owen 2006) showed that to achieve 100(1-β)% power the sample size per treatment arm should be

$$n_{Main} \geq \frac{2s^2[t^{-1}(1-\beta,k,g)]^2}{d^2} \quad (1)$$

where t^{-1} is the inverse cumulative non-central t distribution, with degrees of freedom k and non-centrality parameter

$$g = t^{-1}\left(1-\frac{\alpha}{2},\ 2n_{Main}-2,0\right) .$$

where α is the Type I error rate.

Note n_M appears on both sides of the equation (1) so we need iteration to find the solution.

Inflation factor[1] for non-central t method for 5% Type I error

	Power	
Pilot sample size	90%	80%
20	1.156	1.099
40	1.071	1.045
100	1.027	1.017

[1] Relative to the standard calculations with known variance

Much smaller corrections than the UCL approach

Choosing size of the pilot
Fixed rule of thumb for pilot trials

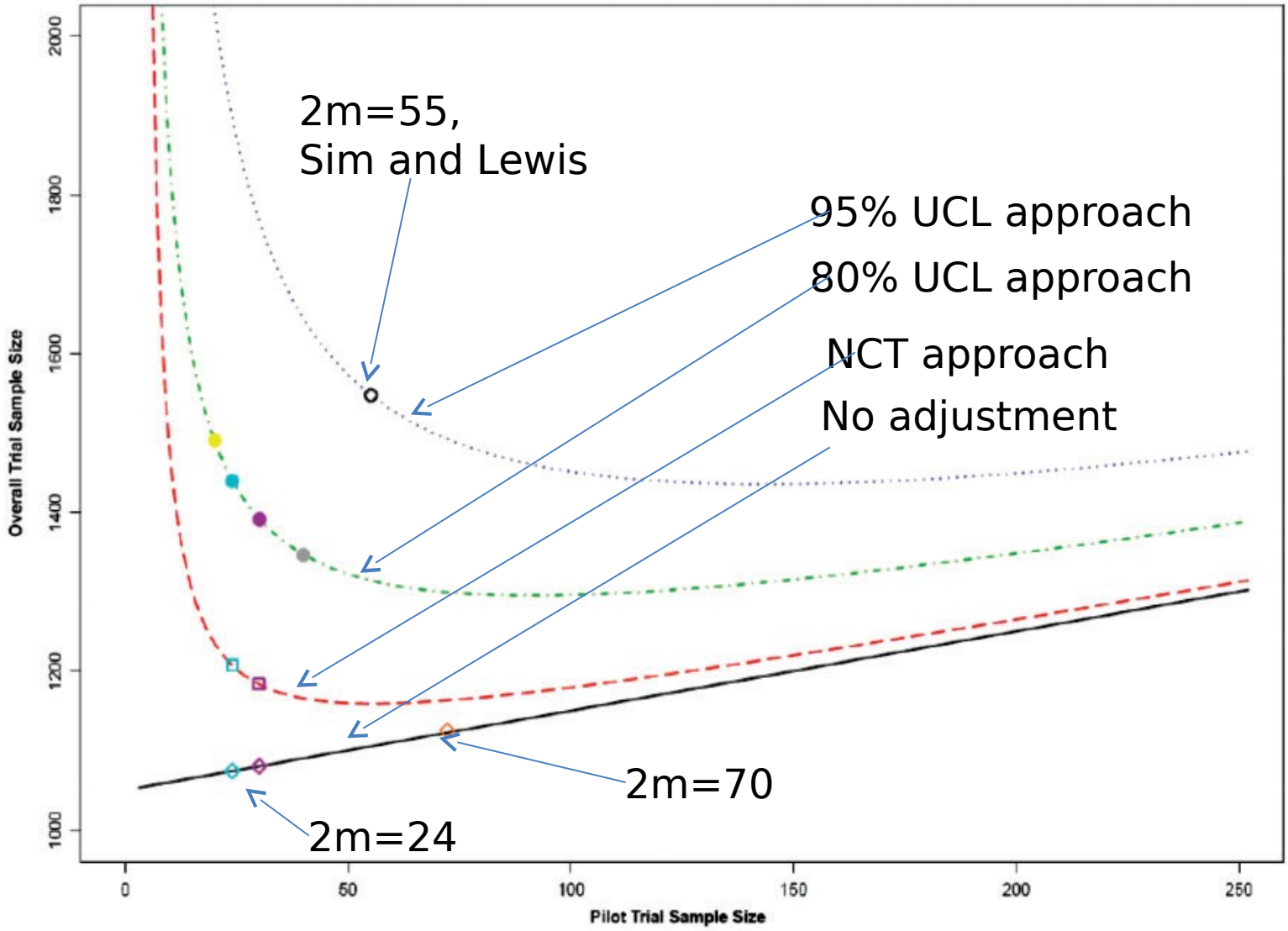
	2m
• Julious (2005)	24
• Browne(1995)	30
• Sim and Lewis (2012)	55
• Teare et al(2014)	70

None of these methods consider minimising the *total* sample size

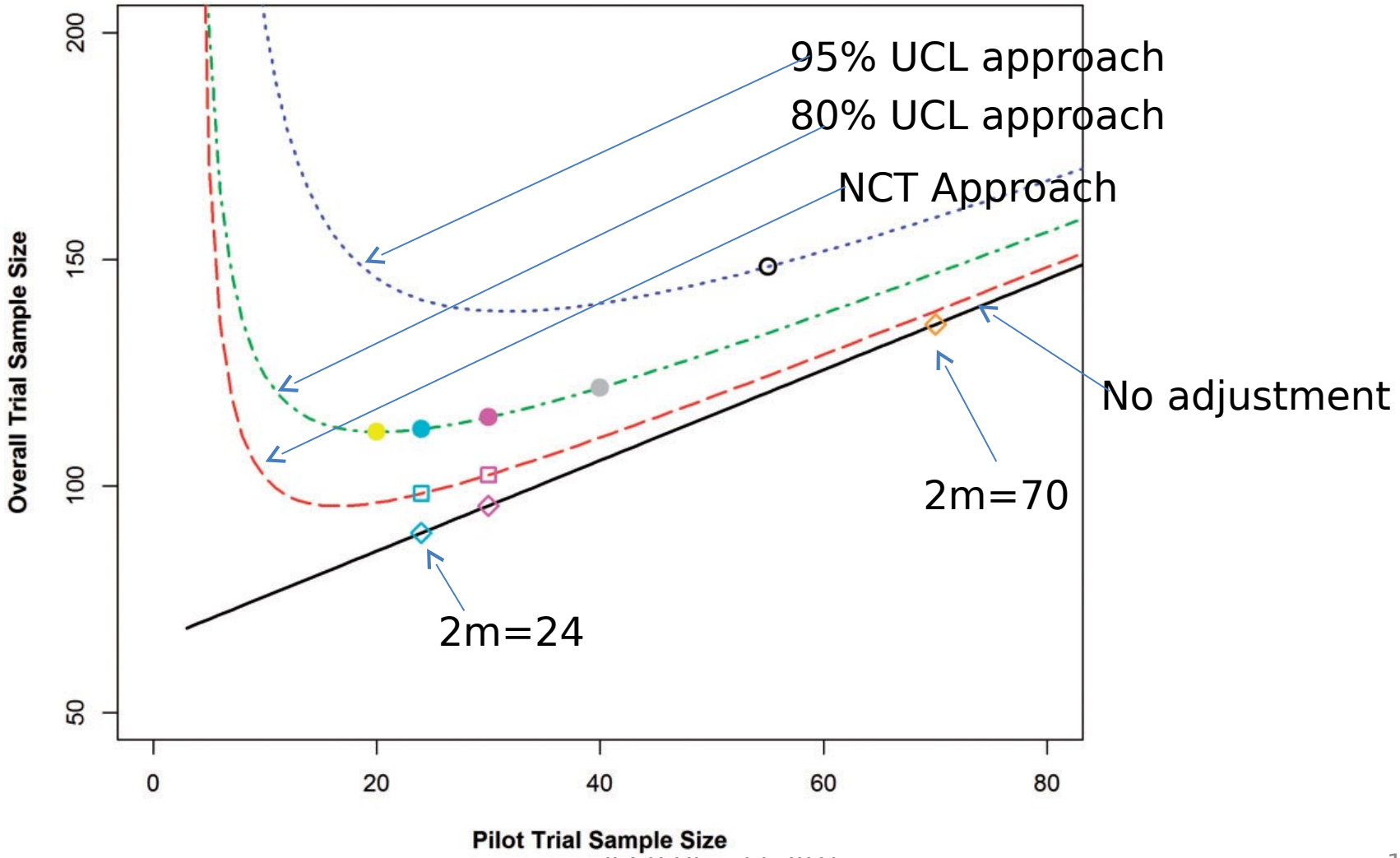
Iterative approach to minimise total sample size $N_{tot} = 2m + 2n_{Main}$

1) Given pilot sample size 2m, and standardised effect size d/s, use traditional sample size formula to find n_{start}
2) Iterate n_{Main} upwards until (1) Slide 9 is satisfied
3) Find $N_{tot} = 2m + 2n_{Main}$
4) Repeat 1-3 for a range of 2m
5) Find $N_{opt} = \min(N_{tot})$

Total trial size for varying pilot trial sizes and a standardised difference



Total trial size for varying pilot trial sizes and a standardised difference of 0.8



Sample sizes per arm, m, for pilot and main trial to give minimum overall with 80% power

	80% UCL			95% UCL			Non central t		
Standardised difference	Pilot	Main	Overall	Pilot	Main	Overall	Pilot	Main	Overall
0.2	39	457	**496**	61	493	**554**	20	412	**432**
0.5	14	83	**97**	22	94	**116**	10[1]	70	**80**
0.8	10[1]	35	**45**	14	42	**56**	10[1]	28	**38**

[1] Lower limit of pilot set to 10

ompare to (say) Julious' rule of thumb (m=12 per ar

Rules of thumb revised (size per arm)

Standardised difference	80% powered main trial	90% powered main trial
$\delta<0.1$	50	75
$0.1<\delta<0.3$	20	25
$0.3<\delta<0.7$	10	15
$\delta\geq0.7$	10	10

Discussion

- Size of the pilot should relate to size of main trial
  - Flat rules of thumb do not do this
- However, sample size estimation is not exact- just need some ‘ball-park figures’
- Need to compromise
  - Large pilot => more precise estimate, but wasted resources
  - Small pilot => less precise estimate, danger of poor estimate of sample size for main trial

Discussion (2)

- Recognise that external pilots have many other purposes (eg estimating recruitment rates, testing willingness to be randomised etc)
- Should not estimate effect size from a pilot.

References

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